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(54) **PROCESS FOR THE PREPARATION AND
PURIFICATION OF THIOL-CONTAINING
MAYTANSINOIDS**

(75) **Inventors:** **Ravi Vankeepuram Jagannatha
Chari, Newton; Wayne Charles
Widdison, Somerville, both of MA
(US)**

(73) **Assignee:** **Immunogen, Inc., Cambridge, MA
(US)**

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(58) **Field of Search** **540/456**

(56) **References Cited**

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Primary Examiner—Bruck Kifle

(74) *Attorney, Agent, or Firm*—Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention provides a process for the preparation and purification of thiol-containing maytansinoids comprising the steps of: (1) reductive hydrolysis of a maytansinoid C-3 ester with a reducing agent selected from the group consisting lithium trimethoxyaluminum hydride (LiAl(OMe)₃H), lithium triethoxyaluminum hydride (LiAl(OEt)₃H), lithium tripropoxyaluminum hydride (LiAl(OPr)₃H), sodium trimethoxyaluminum hydride (NaAl(OMe)₃H), sodium triethoxyaluminum hydride (NaAl(OEt)₃H) and sodium tripropoxyaluminum hydride (NaAl(OPr)₃H) to yield a maytansinol; (2) purifying the maytansinol to remove side products when present; (3) esterifying the purified maytansinol with a carboxylic acid to yield a mixture of an L- and a D-aminoacyl ester of maytansinol; (4) separating the L-aminoacyl ester of maytansinol from the reaction mixture in (3); (5) reducing the L-aminoacyl ester of maytansinol to yield a thiol-containing maytansinoid; and (6) purifying the thiol-containing maytansinoid.

34 Claims, 5 Drawing Sheets